LARGE-CELL NEUROENDOCRINE CARCINOMA OF THE UTERINE CERVIX — A CLINICOPATHOLOGICAL STUDY OF FIVE CASES

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Objective. The present study describes 5 cases of large-cell neuroendocrine carcinoma (LCNEC) of the uterine cervix, evaluating their clinical features and pathological profiles.

Methods. Clinical data were obtained from the patients' clinical files at the combined gynaecological-oncology unit of Johannesburg Hospital and the University of the Witwatersrand Medical School, Johannesburg, South Africa.

A histopathological diagnosis was obtained after biopsy material from all 5 patients was examined microscopically and subjected to immunohistochemical staining with MNF116 (pankeratin), synaptophysin and chromagranin A, all of which are neuroendocrine markers. Two patients received pelvic radiotherapy only. None of the 5 patients in this series received chemotherapy or underwent surgery.

Results. All 5 patients were adult females, with an average age of 57.3 years. The majority were multiparous, with the most common presenting complaint being vaginal bleeding. Three of the 5 patients presented with advanced-stage cervical carcinoma, with evidence of metastases in 2 of them. Treatment responses and long-term survival in our series proved to be disappointing as 3 of the 5 patients died in less than 6 months. On histopathological examination, all 5 tumours showed features of a high-grade poorly differentiated malignant neoplasm with ulceration and extensive tumour necrosis including trabecular and organoid growth patterns. All 5 neoplasms also showed strong immunoreactivity for MNF116, while their endocrine nature was confirmed by staining for synaptophysin in all cases. None of the tumours showed positive staining for chromagranin A.

Conclusions. LCNECs are rare tumours and distinct from other neoplasms of the uterine cervix. The results of this study reaffirm the biologically aggressive nature of this uncommon tumour and its very unfavourable prognosis.

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Carcinoma of the cervix is the most common cancer in women in the developing world.[1] In South Africa, it comprises 34% of all malignant tumours in black females, including a lifetime risk of 1 in 26,[2] and with more than 20 new cases diagnosed per 100 000 of the total female population (cervical squamous cell carcinoma being the predominant type).[3] Large-cell neuroendocrine carcinomas (LCNECs) of the uterine cervix are rare, unusual and highly aggressive tumours with less than 50 cases reported worldwide.[4-6] They are distinct from other tumours of the uterine cervix and appear to be more common than is generally accepted, and may be misdiagnosed as poorly differentiated adenocarcinoma.[6]

It is important to recognise LCNECs of the cervix since their behaviour closely parallels that of their highly aggressive small-cell counterparts.[4,6,7] At present, LCNECs have a very poor prognosis and as is true for small-cell carcinoma, optimal therapy for LCNECs has yet to be determined.[4,6,7] Following a consensus workshop convened in 1997, endocrine tumours of the uterine cervix are now classified into four categories, namely classic (typical) carcinoid, atypical carcinoid, LCNEC and small-cell carcinoma.[4] As this classification is identical to that for endocrine tumours of the lung, this should lead to a better understanding of the biology, therapy and natural history of this family of tumours. To the best of our knowledge, this is the first time that this very rare tumour, namely LCNEC of the uterine cervix, is being reported on from South Africa.

MATERIAL AND METHODS

Clinical data

Patients were selected from those attending the combined gynaecological-oncology unit at the Johannesburg Hospital and then chosen on the basis of a histopathological diagnosis of LCNEC of the uterine cervix.

Tumours were staged according to the International Federation of Gynaecologists and Obstetricians (FIGO) staging system for carcinoma of the uterine cervix.[8] Clinical data were obtained from the patients' in-hospital clinical files, notes from the radiotherapy department and follow-up notes from the gynaecological oncology unit. Four of the 5 patients had a routine chest radiograph, ultrasound examination of the abdomen and pelvis, complete blood count, as well as urea and electrolyte assessment. One patient also had liver function tests performed. Four of the 5 patients were also tested for HIV

(after informed consent was obtained), a purely departmental protocol not practised or offered routinely throughout South Africa.

Biopsy material

Histological sections of the 5 formalin-fixed, paraffin-embedded biopsy specimens of LCNEC were stained with hematoxylin and eosin, and reviewed using established morphological criteria.[4]

Immunohistochemistry

Additional sections from each biopsy specimen were subjected to a panel of immunohistochemical stains, namely MNF116 (pankeratin), synaptophysin and chromagranin A. The sources and dilutions of the respective markers are given in Table I.

RESULTS

Clinical observations

Clinical details with presentation, treatment and outcome for all 5 patients are summarised in Table II.

All patients were adult females and ranged in age from 42 to 75 years (mean age 57.3 years). One patient did not return for further evaluation and treatment, while another (case 5) refused treatment. Three patients were postmenopausal. Reproductive history was obtainable from 4 patients, all of whom were multiparous. The most common presenting complaint was vaginal bleeding. One premenopausal patient (case 2) also complained of postcoital bleeding.

Other complaints included lower abdominal pain, lower back pain, vaginal discharge and weight loss. The cachexia was especially marked in 2 patients (cases 1 and 4). Three patients presented with advanced stage disease, namely stage 3b and 4b. The second patient had evidence of lung metastases on a chest radiograph, while the fourth had evidence of liver metastases on abdominal ultrasound examination and abnormal liver function tests. Two patients received pelvic radiation, while another died before any treatment plan was instituted for her. Patient 2 died 2 weeks after her diagnosis was confirmed, while patients 4 and 1 died within 1 and 3 months respectively, despite pelvic radiotherapy. Patients in this series did not undergo any surgery, nor did they receive any chemotherapy.

Light microscopy

All 5 tumours showed features of a high-grade, poorly differentiated malignant epithelial neoplasm with ulceration and extensive tumour necrosis. The pattern of growth in case 1 was predominantly organoid, while in case 3 the tumour appeared more trabecular and cord-like, with haphazard infiltration of the cervical stroma. Case 2 showed a combination of the growth patterns observed in cases 1 and 3. Case 4 was composed predominantly of large, solid basaloid neoplastic islands. Case 5 showed closely packed broad trabeculae as well as solid basaloid islands and narrow trabecular structures similar to those observed in case 3. Peripheral palisading by tumour cells was a conspicuous feature in areas with a more solid, organoid appearance. The individual neoplastic cells were relatively large, with ill-defined intercellular borders, moderate amounts of pale eosinophilic cytoplasm and

Table I. List of immunohistochemical stains

Antibody	Source	Dilution	Method
MNF 116	Dako, Glostrup, Denmark	1:100	StreptABC/HRP (Duet)
Synaptophysin	Dako, Glostrup, Denmark	1:20	StreptABC/HRP (Duet)
Chromagranin A	Dako, Glostrup, Denmark	1:100	ABC

ABC = avidin biotin complex; HRP = horseradish peroxidase.

Table II. Clinical presentation of patients with cervical LCNEC

Patient/case number	Age (yrs)	Parity	HIV	Stage	Treatment	Outcome
1	75	5	Negative	3b	DXT	Dead — 3 months
2	51	5	Negative	4b	Nil	Dead — 2 weeks
3	42	NA	NA	NA	Nil	LFU
4	65	6	Negative	4b	DXT	Dead — 1 month
5	55	3	Negative	2b	Nil	Alive to date, but refusing treatment

NA = not available; DXT = radiation therapy; LFU = lost to follow-up.

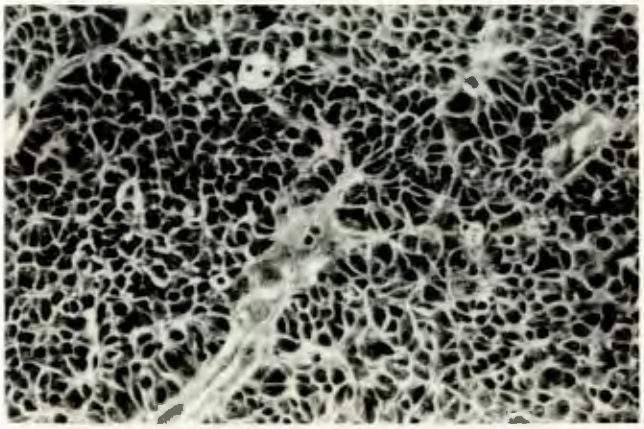

Fig. 1. High-power view of cervical large-cell neuroendocrine carcinoma (case 5). Note ill-defined cellular rosettes, and large pleomorphic tumour cells showing brisk mitotic activity.

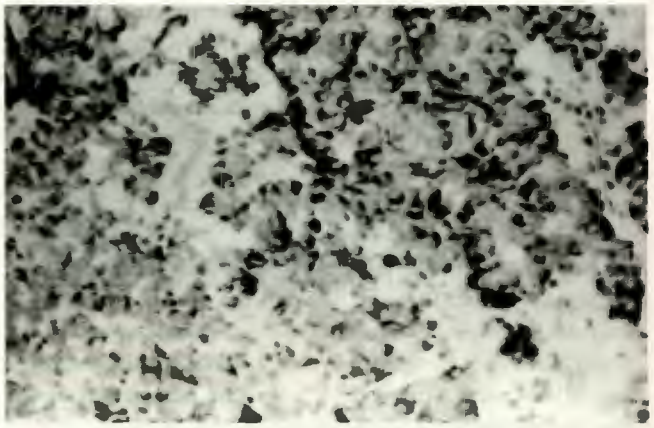

Fig. 2. Cervical large-cell neuroendocrine carcinoma stained with pankeratin marker, MNF116. Note characteristic paranuclear dot-like accentuation of staining pattern.

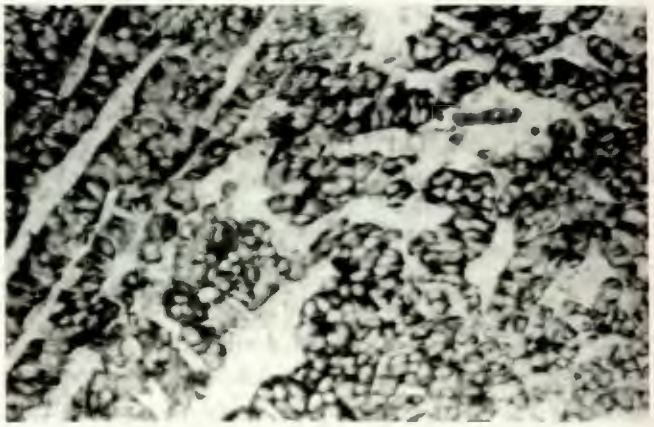

Fig. 3. Strong immunostaining for synaptophysin, confirming the neuroendocrine nature of the carcinomatous lesion, which also exhibits conspicuous trabecular morphology.

pleomorphic round to oval nuclei with irregular nuclei contours, a vesicular to slightly stippled chromatin pattern, and prominent nucleoli (Fig. 1). Occasional ill-defined rosettes were discernible in cases 4 and 5. Apoptotic tumour cells were seen throughout, and there was brisk mitotic activity, with all 5 neoplasms showing in excess of 10 mitoses per 10 high-power fields (HPF), including atypical mitotic figures (MFs). Case 1 showed scattered tumour cells containing intracytoplasmic hyaline globules of varying size. Biopsy-related crush artefact was a conspicuous feature in case 3. Cases 1 and 3 showed microscopic foci of malignant squamous differentiation. All cases showed extensive ulceration of the surface epithelium. Small areas of residual benign, non-dysplastic squamous mucosa were, however, seen in cases 1 and 2. An associated small-cell neuroendocrine carcinomatous component was not observed in any of the neoplasms.

Cases 1, 3 and 4 also harboured microscopic basaloid tumour islands somewhat reminiscent of those encountered in adenoid basal carcinoma of the cervix. An unusual observation in case 3 was the focal presence of small non-congophilic cylinders of hyaline, eosinophilic basement membrane-like material enveloped by the neoplastic epithelial cells.

Immunohistochemistry

All 5 cases showed immunoreactivity for MNF116, with characteristic paranuclear dot-like accentuation of the staining pattern (Fig. 2). The neuroendocrine nature of the neoplasms was confirmed with diffuse staining for synaptophysin, which was moderate in cases 1 - 4, and strongly positive in case 5 (Fig. 3). None of the 5 tumours showed positive staining for chromagranin A.

Discussion

Tumours of the uterine cervix showing neuroendocrine differentiation are rare but distinctive neoplasms.[4,6,7,9,10] It has been proposed that these neoplasms may arise from cells containing neuroendocrine granules that are demonstrable in 20% of normal cervices.[7] Albores-Saavedra and associates reported the first case in 1972, namely a primary carcinoid of the uterine cervix.[4,7] However, cervical neuroendocrine carcinomas other than those of the small-cell type have received little attention and were not recognised as a specific entity in the World Health Organisation (WHO) classification, except for the category of 'carcinoid tumour'.[7]

LCNECs of the uterine cervix are now a well-recognised specific entity[4] and are considered to be more common than is generally appreciated, even though fewer than 50 cases have been reported worldwide.[5-7] Cervical LCNECs have been reported in women aged 21 - 62 years (mean age 34 years).[7] The patients presented with an abnormal Pap smear or vaginal bleeding.[7] These neoplasms are biologically aggressive tumours that are frequently misdiagnosed,[7] and are associated with a poor prognosis and a high mortality rate.[6,7] Their clinical course parallels that of small-cell carcinoma with widespread

dissemination and distant metastasis occurring early on in the disease process.[6,7] Optimal treatment for LCNECs has not yet been determined and response of metastases to chemotherapy is disappointing.[7] In a previously published report,[7] 20 of 31 patients (65%) died of disease, typically within 3 years of diagnosis. In the same series, extra-abdominal metastases were frequently observed, involving lungs and occasionally the brain.[7] In the present study, the mean age of the 5 patients was 57.3 years. All 5 patients presented with vaginal bleeding as a common symptom. Three of the 5 patients presented with advanced stage cervical carcinoma, with metastases to the lung in case 2 and liver metastases in case 4. Patients 1, 2, 4 and 5 were HIV-negative. Long-term survival and prognosis in our series of patients proved to be disappointing, despite radiotherapy in patients 1 and 4. One patient (case 5) refused treatment.

Of the 4 newly categorised tumours of the uterine cervix, LCNEC is biologically and morphologically similar to small-cell carcinoma and atypical carcinoid of the cervix.[4] The most easily applied and reproducible criterion for distinguishing LCNEC from atypical carcinoid is the mitotic rate, that is the number of MFs per 10 HPFs.[4,6]

Characteristically, LCNECs show greater mitotic activity (> 10 MF/10 HPF) accompanied by a higher grade of nuclear atypism, typically more extensive necrosis and positive staining for neuroendocrine markers.[6,7] In the present series, light microscopy revealed extensive tumour necrosis in all 5 cases, with tumours showing organoid, trabecular and/or cord-like growth patterns and hence fulfilling the diagnostic criteria laid down by Albores-Saavedra and associates.[4] All 5 tumours displayed large individual neoplastic cells with abundant cytoplasm, irregular vesicular nuclei and prominent nucleoli. In addition, the 5 neoplasms showed in excess of 10 mitoses per 10 HPFs. The neuroendocrine nature of the neoplasms was confirmed by a positive immune reactivity for synaptophysin, although none of the 5 tumours in this series showed positive staining for chromagranin A, a phenomenon that has been reported on by other authors.[6,7,11] In addition to the above findings, microscopic foci of malignant squamous differentiation were present in cases 1 and 3. In a recent report it has been reaffirmed that all histological categories of endocrine tumours of the uterine cervix can be associated with squamous cell carcinoma or an adenocarcinoma.[12] Currently there is no evidence to suggest that these foci influence the prognosis of LCNEC. It has been postulated that these mixed tumours may arise from divergent differentiation of neoplastic cells, or may represent separate primary tumours.[12] None of the neoplasms in this series showed an associated small-cell neuroendocrine carcinomatous component, although other authors have mentioned this coexistence.[5,13]

In conclusion, cervical LCNECs are distinctive, unusual and aggressive neoplasms that are frequently misdiagnosed and have a very poor prognosis. Their recognition is important, as it will allow an evaluation of appropriate therapies that may improve their unfavourable outcome. Equally important is the use of uniform diagnostic terminology, as this will enable us to understand clearly their natural history and biological behaviour, and to estimate the incidence of this rare and virulent cervical cancer.

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